Tenapanor Treatment Success for IBS-C Symptoms Increases With Duration of Therapy

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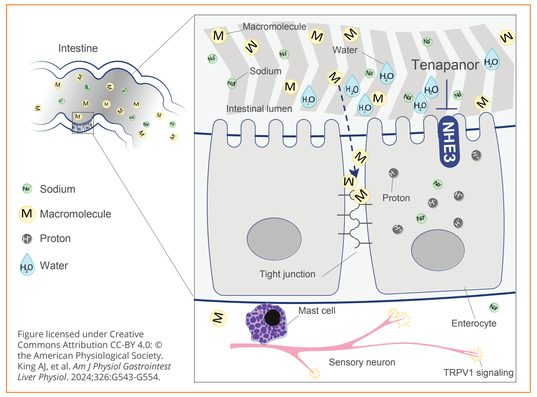
Introduction

- Irritable bowel syndrome with constipation (IBS-C) is a common disorder of gut-brain interaction characterized by abdominal pain and altered bowel habits (eg, reduced stool frequency, hard/lumpy stools).[1,2]
- Tenapanor is a first-in-class, minimally absorbed, small-molecule inhibitor of intestinal sodium/hydrogen exchanger isoform 3 (NHE3) and is approved by the Food and Drug Administration for adults with IBS-C.[3,4]
- In multiple prospective, controlled clinical trials, tenapanor 50 mg twice a day (bid) significantly increased complete spontaneous bowel movements (CSBM) and reduced abdominal symptoms compared with placebo in patients with IBS-C.[5-7]
- We conducted a post hoc analysis of pooled data from the phase 2b (NCT01923428) and phase 3 T3MPO-1 (NCT02621892) and T3MPO-2 (NCT02686138)[5-7] studies to evaluate time to onset of tenapanor effect on bowel function and abdominal symptoms in patients with IBS-C.

Mechanism of Action of Tenapanor

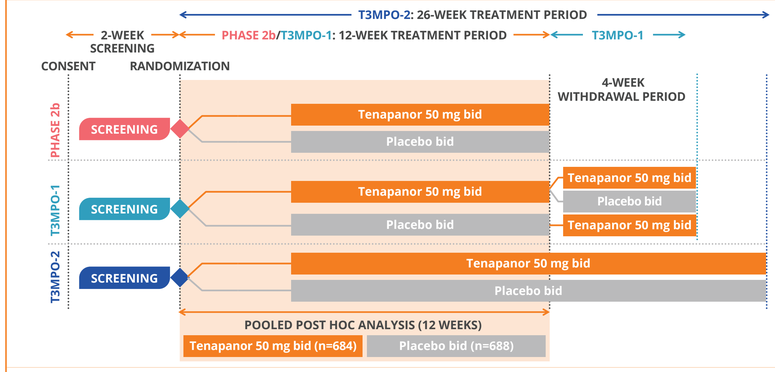
- Tenapanor inhibits NHE3, leading to:
  - Reduction of dietary sodium absorption, which in turn leads to retention of fluid in the intestinal lumen, resulting in softer stool consistency and accelerated intestinal transit.[4,8,9]
  - Decreased intestinal permeability to macromolecules in nonclinical studies.[10]
  - Reduced visceral hypersensitivity and abdominal pain in nonclinical studies.[10]



Methods

- Study methods have been described previously for all studies.[5-7]
- Patients were randomized to tenapanor 50 mg or placebo bid for 12 (phase 2b and T3MPO-1) or 26 (T3MPO-2) weeks (**Figure 1**).[5-7]
- A phone diary was used to collect data on daily CSBMs and abdominal symptoms (pain, bloating, and discomfort; each on a scale from 0-10) (**Figure 2**).[5-7]
- Based on the pooled data within the first 12 weeks of the randomized treatment period in the 3 studies, the Kaplan-Meier method was used to analyze the following:
  - Time to first onset of weekly CSBM response (ie, achieving an increase of ≥1 from baseline in average weekly CSBMs).
  - Time to first onset of weekly abdominal pain, bloating, and discomfort responses (ie, achieving a decrease of ≥30% from baseline in average weekly score of the corresponding abdominal symptom).
- Intent-to-treat (ITT) patients with valid weekly data were included in this analysis.

Figure 1: Study Design



bid, twice a day.

Figure 2: Interactive Voice Response System Diary

The IVRS diary collected information on daily stool frequency, stool consistency, straining, abdominal pain, abdominal discomfort, abdominal bloating, abdominal fullness, abdominal cramping, and rescue medication usage. IBS severity and constipation severity were assessed weekly through the IVRS diary.[a]

Example questions[b]:

How would you rate your worst abdominal pain over the past 24 hours?
...your abdominal discomfort over the past 24 hours?
...your abdominal bloating over the past 24 hours?
...your abdominal cramping over the past 24 hours?
...your abdominal fullness over the past 24 hours?

Questions were assessed separately using the following scale for responses:

0	1	2	3	4	5	6	7	8	9	10
None										Very Severe

[a]Entries into the IVRS diary must have been recorded between 6:00 PM and 11:59 PM (local time). [b]Example questions reflect questions relevant to the analysis presented. The full IVRS diary included 4 weekly questions and 7 daily questions (with sub-questions for each bowel movement and each use of rescue medication).
IBS, irritable bowel syndrome; IVRS, Interactive Voice Response System Diary.

Results

- The pooled population included 1372 intent-to-treat patients (688 placebo, 684 tenapanor).
- Patient demographics and baseline characteristics were generally similar between groups (**Table 1**).

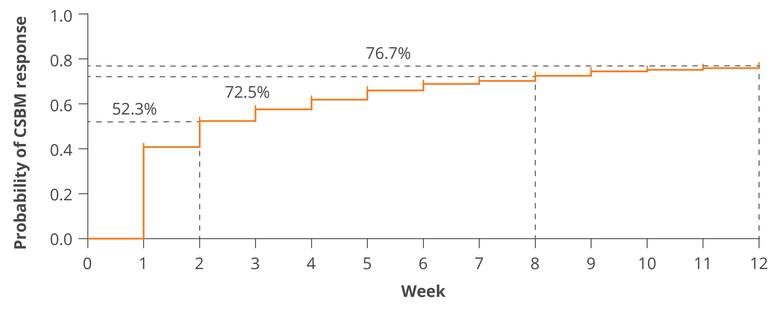
Table 1: Patient Demographics and Baseline Characteristics (Pooled Population)

	Placebo (n=688)	Tenapanor 50 mg bid (n=684)	Overall (n=1372)
Age, mean (SD), y	45.0 (13.5)	45.7 (13.1)	45.3 (13.3)
Sex, n (%)			
Female	572 (83.1)	559 (81.7)	1131 (82.4)
Race, n (%)			
Asian	14 (2.0)	24 (3.5)	38 (2.8)
Black or African American	214 (31.1)	195 (28.5)	409 (29.8)
White	442 (64.2)	452 (66.1)	894 (65.2)
Other	18 (2.6)	13 (1.9)	31 (2.3)
Body mass index, mean (SD), kg/m²	29.9 (6.8)	30.0 (7.0)	30.0 (6.9)
Duration of IBS symptoms before randomization, mean (SD), y[a]	11.6 (11.9)	11.2 (11.6)	11.4 (11.7)
Baseline weekly score for abdominal symptoms and CSBM, mean (SD)			
Pain	6.27 (1.65)	6.24 (1.67)	6.25 (1.66)
Discomfort	6.45 (1.68)	6.45 (1.67)	6.45 (1.67)
Bloating	6.57 (1.82)	6.61 (1.77)	6.59 (1.79)
CSBM frequency	0.16 (0.40)	0.16 (0.42)	0.16 (0.41)

[a]Six patients in the T3MPO-1 study did not report the start date of their IBS symptoms. Thus, the mean (SD) duration of IBS symptoms before randomization of the pooled population is reported for the following numbers of patients: placebo (n=684), tenapanor (n=682) and overall (n=1366).
bid, twice daily; CSBM, complete spontaneous bowel movement; IBS, irritable bowel syndrome.

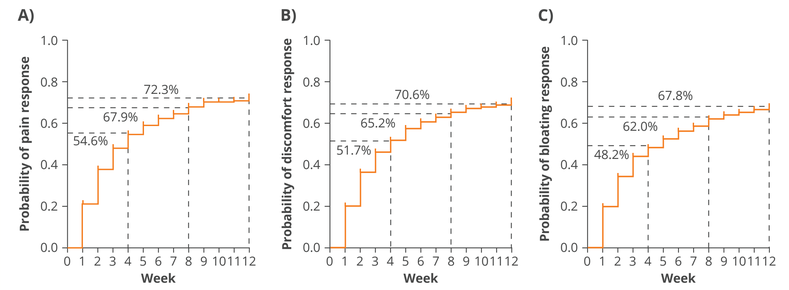
- The median time to first onset of weekly CSBM response with tenapanor (n=664) treatment was 2 weeks.
- The estimated probability of achieving the first CSBM response with tenapanor treatment by week 2 was 52.3%, by week 8 was 72.5%, and by week 12 was 76.7% (**Figure 3**).
- The median time to first onset of weekly response with tenapanor treatment was 4 weeks for abdominal pain (n=664), 4 weeks for abdominal discomfort (n=664), and 5 weeks for abdominal bloating (n=663) (**Figure 4A-C**).

Figure 3: Estimated Probability of Achieving the First CSBM Response[a]



[a]CSBM response was defined as achieving an increase of ≥1 in average weekly CSBMs from baseline.
CSBM, complete spontaneous bowel movement.

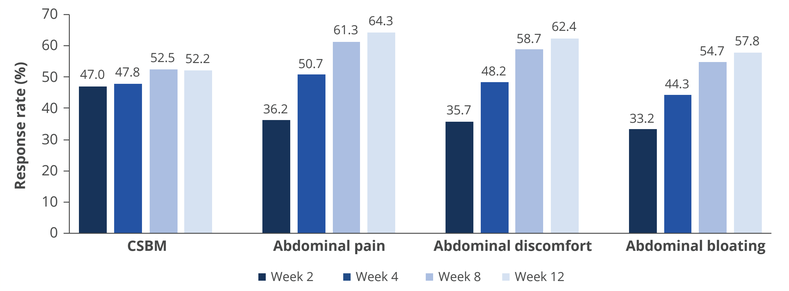
Figure 4: Estimated Probability of Achieving the First (A) Pain, (B) Discomfort, and (C) Bloating Response[a]



[a]Response was defined as achieving a decrease of 30% or more in average weekly abdominal score from baseline.

- The weekly response rates for abdominal pain, bloating, and discomfort increased with treatment duration (**Figure 5**).

Figure 5: Response Rates With Tenapanor Treatment at Weeks 2, 4, 8, and 12[a]



[a]CSBM response was defined as achieving an increase of ≥1 in average weekly CSBMs from baseline, and abdominal pain, bloating, and discomfort response was defined as achieving a decrease of 30% or more in average weekly abdominal score from baseline.
CSBM, complete spontaneous bowel movement.

Safety

- Safety outcomes for tenapanor studies in IBS-C have been previously reported.[5-7]
- Diarrhea was the most commonly reported adverse event, which was mostly mild to moderate in severity.
- Tenapanor was shown to be generally well tolerated, with an acceptable safety profile.

Conclusions

This pooled post hoc analysis of 3 placebo-controlled studies indicates that adult patients with IBS-C experience a relatively quick onset of symptom relief under tenapanor treatment, as shown by the median time to first response for CSBM (2 weeks), abdominal discomfort (4 weeks), abdominal pain (4 weeks), and abdominal bloating (5 weeks).

Weekly response rates continued to increase with treatment duration, with 52.2% of patients achieving CSBM response and 57.8% to 64.3% of patients achieving an abdominal symptom response in week 12.

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Disclosures

Brian E. Lacy is a consultant for Ironwood, Salix, and Viver.
David P. Rosenbaum and Yang Yang are employees of Ardelyx, Inc.

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